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From: Edwin V. Merkel	Date: May 10, 2007	No. of Pages: 14 (including this page)	

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From: Edwin V. Merkel	Date: May 10, 2007	No. of Pages: 14 (including this page)	Client/Matter: 2354/141
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The USPTO has received your submission at **17:04:39** Eastern Time on **13-APR-2007** by Deposit Account: 141138.

$ 225 fee paid by e-Filer via *RAM* with Confirmation Number: 724.

eFiled Application Information

EFS ID	1681835
Application Number	10053088
Confirmation Number	6479
Title	Antimicrobial polymeric compositions and method of treatment using them
First Named Inventor	Graham John Hamilton Melrose
Customer Number or Correspondence Address	Michael L. Goldman NIXON PEABODY LLP Clinton Square P.O. Box 31051 Rochester NY 14603 US 7162631600
Filed By	Tate L. Tischner.
Attorney Docket Number	2354/141 (FF34527/02)
Filing Date	18-JAN-2002
Receipt Date	13-APR-2007
Application Type	Utility

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Application Details

Submitted Files	Page Count	Document Description	File Size	Warnings
20070413_Request_for_Reconsideration_2354_141.pdf	9	Applicant Arguments/Remarks Made in an Amendment	122951 bytes	◆ PASS
fee-info.pdf	2	Fee Worksheet (PTO-06)	8195 bytes	◆ PASS

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Electronic Patent Application Fee Transmittal

Application Number:	10053088
Filing Date:	18-Jan-2002
Title of Invention:	Antimicrobial polymeric compositions and method of treatment using them
First Named Inventor/Applicant Name:	Graham John Hamilton Melrose
Filer:	Tate L. Tischner/Jo Ann Whalen
Attorney Docket Number:	2354/141 (FF34527/02)

Filed as Small Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	225	225

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	225

PATENT
Docket No.: 2354/141

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Melrose et al.	Examiner: Preeti Kumar
Serial No.	:	10/053,088	Art Unit: 1751
Cnfrm. No.	:	6479	
Filed	:	January 18, 2002	
For	:	ANTIMICROBIAL POLYMERIC COMPOSITIONS AND METHOD OF TREATMENT USING THEM	

REQUEST FOR RECONSIDERATION

Mail Stop AF
Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action mailed November 17, 2006, for the above-identified application, applicants respectfully request reconsideration of the rejection set forth therein and withdrawal of finality for the reasons presented below.

As noted at page 7 of the preceding amendment, dated August 30, 2006, applicants re-introduced the subject matter of prior claim 1 (from the amendment dated May 31, 2005) due to the retraction of allowability by the U.S. Patent and Trademark Office ("PTO"). In other words, claim 48 as presented with the amendment dated August 30, 2006, is identical to claim 1 as it existed on May 31, 2005.

With the outstanding office action, the PTO has rejected the subject matter of claim 48 for the first time over PCT Application WO 96/38186 to Melrose ("Melrose I"). Melrose I was cited by the applicants in an information disclosure statement filed on February 16, 2004. Thus, the PTO could have rejected the subject matter of claim 48 in the office actions dated November 30, 2004, and August 25,

2005. No such rejection was ever made. With the outstanding office action, the PTO for the first time imposed a rejection of the subject matter of claim 48 over Melrose and made the office action final. This is improper. The preceding amendment did not necessitate the rejection given that the PTO could have raised the rejection before, but did not.

For this reason, the finality of the outstanding office action should be withdrawn.

The rejection of claims 2-7, 9-13, 15-17, 24-39, 42, and 44-48 under 35 U.S.C. §§ 102(b), 103(a) as anticipated by or for obviousness over Melrose I is respectfully traversed.

The present application describes and claims "A polymeric antimicrobial composition comprising *a derivative of poly(2-propenal, 2-propenoic acid) having protected carbonyl groups formed by reaction between a poly(2-propenal, 2-propenoic acid) and an organic compound containing one or more hydroxyl groups under conditions effective to form said derivative of poly(2-propenal, 2-propenoic acid) having protected carbonyl groups.*" Claim 48 (emphasis added).

Melrose I teaches the formation of poly(2-propenal, 2-propenoic acid) and its use to treat or prevent gastrointestinal disease in various animals. Thus, Melrose I merely describes how to form the starting material that can be used to form the claimed composition.

While Melrose I discloses the poly(2-propenal, 2-propenoic acid) from which the recited derivative may be formed, Melrose I does not disclose formation of the recited derivative. Briefly, Melrose I fails to teach or suggest reacting poly(2-propenal, 2-propenoic acid) and an organic compound containing one or more hydroxyl groups under conditions effective to form the recited derivative, which has protected carbonyl groups.

As discussed in great detail below, the manner by which the present invention was made and the examples of the present application—showing unexpected properties—clearly demonstrate that the presently claimed invention is both novel and non-obvious over Melrose I.

The present application explains that formation of the recited derivatives uses conditions normally associated with accelerated aging studies. Page 20 of the application recites:

> The invention has been found to significantly increase the stability of poly(2-propenal, 2-propenoic acid) polymers. Since the prior art recorded some instability of poly(2-

propenal, 2-propenoic acid), as evidenced by loss of antimicrobial activity of its compositions, we conducted "accelerated ageing" at elevated temperature, ie. at 40°C. However, to our greatest surprise, the elevated temperature of "ageing" poly(2-propenal, 2-propenoic acid) in aqueous or in aqueous-polyethylene glycol solutions at 40°C, not only slowed the decrease in antimicrobial activity-but in fact, actually increased antimicrobial activity of the poly(2-propenal, 2-propenoic acid), see Example 2(a) and (b). This finding is totally contradictory and unexpected in view of the prior art which predicts that the rise in temperature should lead to "accelerated ageing", ie. accelerated loss of antimicrobial activity.

Poly(2-propenal, 2-propenoic acid), the starting material for the claimed composition, can be prepared in the manner described by Melrose I. One approach for the manufacture of poly(2-propenal, 2-propenoic acid) is described in Melrose I as follows:

> Particularly, carefully heating the Subject Polymers formed by ionic initiation/catalysis *with ample air from room temperature to up to 100°C and preferably up to 80-85°C*, produces the Subject Polymers having 0.1-5 moles of carboxyl groups/kg, aqueous soluble at the pH of the duodenum especially, and preferred for the applications in gastrointestinal tracts described and envisaged herein.

See Melrose I at page 3, lines 22 to 30 (emphasis added). The specific exemplification of such preparation of poly(2-propenal, 2-propenoic acid) is in Example 1b of Melrose I, which recites:

> (b) Using an ionic initiator/catalyst: 1.6 g distilled acrolein was made up to 20ml with deionised water in a 200 ml beaker and then, ca. 0.5ml of 0.2M sodium hydroxide added with stirring to pH ca. 10-11. The solution became cloudy and a white principate began to form. The contents were stirred for a further 2 hours and then filtered. The precipitate was washed thoroughly with deionised water until the filtrate was neutral. *The product may be carefully heat-dried in contact with ample air, initially at ambient temperatures and then at temperatures up to about 100°C. Alternatively, as in this case, the product may be dried under vacuum to a white-pale yellow, fine powder; dissolved in methanol, and it may be evaporated down to dryness and then again, dissolved in methanol or other solvents.* Often, the Subject Polymers have 0.1-5 moles of carboxyl groups/kg and were found to have GPC retention times which were mainly shorter than that of polyethylene glycol 2,000. ^{13}C-NMR (300MHz) δ(relative to d_4-methanol at 49.00): 19-31 (CH_2); 35.95 (CH_2); 37-42 (CH); 62-73 (CH_2); 73-81 (CH); 92-95 (CH); 96-103 (CH); 114-120 (CH_2); 134-141 (CH); 196.0 (CH).
>
> In experiments using in each case, 2 groups of 10 Swiss white mice (treated and control, respectively) it was found that solutions of the Subject Polymers in aqueous triethanolamine adjusted to pH 8, had an acute intra-venous toxicity of 320mg/kg, and acute oral toxicity of > 5000mg/kg (no deaths nor abnormal signs were apparent over 14 days).

See Melrose I at page 8, line 36 to page 9, line 17 (emphasis added). From the above descriptions, it is clear that the poly(2-propenal, 2-propenoic acid) is not heated with polyethylene glycol or other alcohol, or reacted with any organic compound containing one or more hydroxyl groups under conditions effective to cause formation of the recited derivative). Neither the specification nor the examples suggest such a procedure.

On page 4 of the office action the PTO points to the fact that in the polymeric unit of formula I the substituent R is H or alkyl (usually C_1 to C_4 alkyl). However, such groups are formed during polymerization by use of a monomer incorporating acetal functionality, such as in Example 4 where acrolein diethyl acetal is used as a monomer. Further, the PTO should note that polyacrolein is itself a mixture of acetal and hemiactal forms, which arises from the fact that acrolein may undergo polymerization via carbon-carbon chain extension or by carbon-oxygen chain extension. As explained in several other submissions by the applicants, these acetal and hemiacetal forms are clearly different from the acetal and hemiacetal forms present in the derivatives of the invention, because the acetals and hemiacetals formed during polymerization (which are referred to in the citation) are part of the polymer backbone rather than part of the recited carbonyl protecting groups.

As explained on pages 5-6 of the present application (and required by claim 1), the acetals/hemiacetals provided in the derivative of the invention form the protected carbonyl groups from the groups of formula I in the backbone.

Accordingly, there is a clear structural difference between the poly(2-propenal, 2-propenoic acid) disclosed in Melrose I, which is formed by heating polyacrolein in air, and the derivative recited in the presently claimed invention, which can be formed by heating poly(2-propenal, 2-propenoic acid) for a sufficient time and temperature in the presence of organic compounds having one or more hydroxyl groups. This structural distinction is supported by the fact that the properties of the claimed composition are improved relative to the poly(2-propenal, 2-propenoic acid) of Melrose I.

Examples 10 and 11 of the present application describe the preparation and compare the efficacy of poly(2-propenal, 2-propenoic acid) and the derivative of the present invention. In Example 10a, poly(2-propenal, 2-propenoic acid) is prepared in accordance with the general procedure of Example 1b of Melrose I. In part 2 of Example 10(a), polyacrolein is prepared using an ionic catalyst (sodium hydroxide) in water. In part 4 of this same example, the polyacrolein is dried and oxidized in air to provide poly(2-propenal, 2-propenoic acid). Example 10(b) describes the preparation of an acetal derivative formed between poly(2-propenal, 2-propenoic acid) and polyethylene glycol, which occurs by

heating at 100°C for 4 hours. Example 11 demonstrates that the derivative composition of the claimed invention (prepared in Example 10b) has a statistically significant improvement in activity against gastrointestinal disease when compared with poly(2-propenal, 2-propenoic acid) of Melrose I (prepared in Example 10a).

Thus, from the description in the present application and the comparative examples, the poly(2-propenal, 2-propenoic acid) of Melrose I and the recited derivative of the claimed composition are structurally distinct and possess different activity.

Despite this structural and functional distinction between the poly(2-propenal, 2-propenoic acid) of Melrose I and the recited derivative of the claimed composition, the PTO appears to take the position that Melrose I inherently teaches the presently claimed invention because of the conditions employed in Melrose I. Applicants disagree.

Examples 3 and 4 of the present application demonstrate that conversion to the derivative requires heating of poly(2-propenal, 2-propenoic acid) with the organic compound containing one or more hydroxyl groups (e.g., an alcohol) for a significant period. The mere dissolution of the starting polymer in alcohol does not of itself provide the derivative. Thus, the PTO's reference to Melrose I compositions of poly(2-propenal, 2-propenoic acid) in an alcohol does not inherently teach the derivative of the invention, because—as demonstrated in Examples 3 and 4 of the present application—specific additional steps would be necessary. Those steps, heating for an extended period, cannot be regarded as inherent or obvious as the citation merely teaches the alcohol as a carrier. Without the benefit of hindsight, there would be no reason to expect an advantage from any chemical reaction. (Indeed, as explained above, it was even expected initially by the applicants that heating for any period would merely accelerate aging and bring about a reduction in activity.)

Applicants do not understand the PTO's position asserted in the paragraph bridging pages 4 and 5 of the office action. The language does not appear to relate to Melrose I but rather to WO 00/03723, which the PTO cited in previous office actions but not in the present office action (*see* Office Action of 15 March 2006 on page 3, at item 10). Thus, these comments appear to have been erroneously lifted from portions of the previous office action relating to WO 00/03723 and, hence, have not been addressed.

In the final paragraph on page 5 of the outstanding office action, the PTO refers to the description in Melrose I of the preparation of pellets comprising poly(2-propenal, 2-propenoic acid). The pellets contain acid groups, but these acid groups are present in carrier polymer. The acid groups referred to are not in the subject polymers. Thus, in this instance, Melrose I does not inherently teach the claimed derivative composition.

On pages 6-7 of the outstanding office action, the PTO references various passages of Melrose I where dosage formulations of poly(2-propenal, 2-propenoic acid) are recited as including polyethylene glycol, among other organic compounds that contain one or more hydroxyl groups. However, the description in Melrose I is merely that of a dosage formulation, not a reaction step. Given the above-noted results of Examples 3, 4, 10, and 11 of the present application, it is improper to assume that such dosage formulations inherently contain the recited derivative. Indeed, as stated above, more is required than mixture of these two compounds; the reaction conditions must also be present. The PTO has failed to demonstrate that those conditions are present under the circumstances recited in Melrose I. Consequently, the cited language of Melrose I does not inherently teach or suggest the claimed composition.

In the penultimate paragraph on page 7 of the office action, the PTO refers to specific examples of Melrose I. It should be recognized that the experimental detail quoted by the PTO does not make poly(2-propenal, 2-propenoic acid) let alone the derivative of the present invention. Example 1 of Melrose I describes the formation of poly(2-propenal, 2-propenoic acid), but not the derivative as recited in claim 48. Thus, Example 1 of Melrose I does not recite a composition as asserted by the PTO on page 7 of the outstanding office action. Example 13 of Melrose I describes the formation of copolymer of acrolein and polyethylene glycol acrylate, but not the derivative as recited in claim 48 let alone the starting polymer of poly(2-propenal, 2-propenoic acid). Although Example 13 of Melrose I recites the conditions noted on page 7 of the outstanding office action, the conditions do not involve combining poly(2-propenal, 2-propenoic acid) with an organic compound containing one or more hydroxyl groups under conditions suitable to form the recited derivative. Specifically, polyethylene glycol acrylate is an ester in which the acid portion is acrylic acid and the alcohol portion is polyethylene glycol. The resulting polymer is a copolymer of the ester monomer and acrolein. It cannot in any sense be described as a derivative of poly(2-propenal, 2-propenoic acid) having protected carbonyl groups formed by reaction between a poly(2-propenal, 2-propenoic acid) and an organic compound containing one or more hydroxyl groups under conditions effective to form the derivative.

Example 15 of Melrose I merely describes administration of poly(2-propenal, 2-propenoic acid), in water, to piglets. This does not involve formation of the recited derivative, let alone conditions effective for its formation.

Consequently, the PTO's conclusion on pages 7-8 of the office action that *"Melrose et al illustrates a composition comprising poly(2-propenal, 2-propenoic acid) in*

polyethylene glycol which is ***substantially identical to the material limitations of the instant claims"*** (emphasis added), is improper and without support.

The PTO's conclusion regarding obviousness of the claimed composition is similarly without support. On page 8 of the outstanding office action, the PTO asserts that the claimed composition would have been obvious "*because Melrose et al. teach a reaction of the subject polymers poly(2-propenal, 2-propenoic acid) with polyethylene glycol at room temperature up to 100 degrees C to increase hydrophilicity and utility in the application of treating diseases of the gastrointestinal tract of human, animals and birds.*"

In support of this conclusion, the PTO cites to page 3, lines 25-35, of Melrose I. However there is no basis whatsoever for the assertion that Melrose I teaches reaction of poly(2-propenal, 2-propenoic acid at room temperature to 100°C. The text cited by the PTO is reproduced below in its entirety:

> Subject Polymers may generally be increased by inclusion within them of hydrophilic groups, especially carboxyl groups, or of hydrophilic monomers, especially acrylic acid. Particularly, carefully *heating the Subject Polymers formed by ionic initiation/catalysis with* ***ample air*** *from room temperature to up to 100°C*, and preferably up to between 80-85°C, produces the Subject Polymers having 0.1-5 moles of carboxyl groups/kg, aqueous soluble at the pH of the duodenum especially, and preferred for the applications in gastrointestinal tracts described and envisaged herein.
>
> The Subject Polymers have the following properties:
>
> The Subject Polymers have an unusually broad *in vivo* antimicrobial profile, providing a method of treatment of gastrointestinal disease in humans, animals or birds.
>
> It has been shown that the Subject Polymers provide increased weight gains in human, animals or birds.

Melrose I at page 3, lines 24-35 (emphasis added). The "Subject Polymers" of Melrose I are not limited to those which contain acid groups and this paragraph is clearly referring to the embodiment in which the polymers are provided with acid group by forming the polymer by ionic catalysis (as demonstrated in Example 1b) and oxidizing in air to form acid groups. There is nothing which teaches forming a derivative of poly(2-propenal,2-propenoic acid) with an organic compound having one or more hydroxyl groups, such as polyethylene glycol, at elevated temperatures to provide protected carbonyl groups. Melrose I likewise provides no such motivation to do so, and the PTO has cited none.

Even if *prima facie* obviousness could be sustained (which applicants submit is improper for the reasons noted above), then the showing of significant advantages in efficacy of the claimed derivatives over poly(2-propenal, 2-propenoic acid) demonstrates that the invention cannot be regarded as obvious.

For all these reasons, the rejection of claims 2-7, 9-13, 15-17, 24-39, 42, and 44-48 as anticipated by or for obviousness over Melrose I is improper and should be withdrawn.

The rejection of claims 2-7, 10, 13, 16, 17, 24-25, 28, 30, 31, 42, and 46-48 for obviousness-type double patenting over claims 1, 10, 18, 22, 24, and 28 of U.S. Patent No. 6,410,040 to Melrose et al. ("Melrose II") is respectfully traversed.

The claims of Melrose II cited by the PTO relate to methods of preparing compositions of poly(2-propenal, 2-propenoic acid). The specification of Melrose II makes clear that the recited method steps are intended to result in a stable solution of poly(2-propenal, 2-propenoic acid) that resists precipitation. Importantly, the claims of Melrose II encompass different statutory classes of subject matter from that which is presently claimed (i.e., compositions and methods of use) and the limitation of the presently claimed invention would not have been obvious over the recited claims of Melrose II, because the claims of Melrose II fail to recite formation of the recited derivative let alone conditions effective to result in formation of the derivative. Absent such showing, the presently claimed compositions and methods of use cannot have been obvious over the claims of Melrose II.

Because the rejection is improper for the reasons noted above, the obviousness-type double patenting rejection over claims of Melrose II is improper and should be withdrawn.

The rejection of claim 2-7, 9-13, 15-17, 24-39, 42, and 44-48 for obviousness-type double patenting over claims 1-36 of U.S. Patent No. 6,723,336 to Melrose ("Melrose III") is respectfully traversed.

Melrose III is related to Melrose I as the corresponding U.S. national phase. Thus, the disclosure of these references is identical. Briefly, Melrose III teaches the formation of poly(2-propenal, 2-propenoic acid) and its use to treat or prevent gastrointestinal disease in various animals. For the same reasons discussed above with respect to Melrose I, Melrose III fails to teach reacting poly(2-propenal, 2-propenoic acid) with an organic

compound containing one or more hydroxyl groups under conditions effective to form the recited derivative, which has protected carbonyl groups.

The cited claims of Melrose III relate to methods for treatment of poultry or piglets, involves administration of the polymers as recited. However, for substantially the same reasons noted above, the presently claimed compositions and their methods of use are neither taught nor suggested in Melrose III, because Melrose III does not describe the underlying derivative of poly(2-propenal, 2-propenoic acid) or the conditions effective for its production.

Thus, the cited claims of Melrose III would not have rendered obvious the presently claimed compositions or the methods of using such compositions.

Because the rejection is improper for the reasons noted above, the obviousness-type double patenting rejection over claims of Melrose III is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: April 13, 2007

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